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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/740,211	12/18/2000	Linda B. Couto	AVIGEN.003C1	4340

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	14

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/740,211	Applicant(s) COUTO ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-17 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 8-17 and 19 are pending examination.

The terminal disclaimer in paper no. 11 and the cancellation of claims 2-7 and 18, the amendment to claims 8 and 9, applicants' traversal in paper no. 13 are acknowledged and considered.

Drawings

The corrected or substitute drawings were received on 4/17/02. These drawings are acceptable.

Information Disclosure Statement

The information disclosure statement filed on 4/21/01 in paper no. 4 does not fully comply with the requirements of 37 CFR 1.98 because: applicants did not correct the date of patent no. 5,255,347 on page 6, which should read 7/6/93.

The examiner has considered the references, but in order to have the patent document initialed and dated on the 1449, a new 1449 properly citing the patent must be filed with the response to this office action. Failure to comply with this notice will result in the above mentioned information disclosure statement being placed in the application file with the non-complying information not being considered. See 37 CFR 1.97(i).

Claim Objections

Claims 14-15 are objected to as being dependent upon a rejected base claim (claim 8), but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Double Patenting

The rejection for claims under the judicially created doctrine of obviousness-type patenting double patenting over claims of U.S. Patent No. 6,200,560 and U.S. Patent No. 6,221,349 are overcome by the terminal disclaimer filed on 4/17/02.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 8-10 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Dwarki et al. (US Patent No. 6,221,646, effective filing date, 7/31/1997). Dwarki teaches a method of producing a replication defective recombinant AAV virions, comprising the following structure: (i) a heterologous gene operatively positioned between two AAV ITRs; (ii) an AAV helper construct having at least one gene encoding an AAV capsid protein, and (iii) an adeno-plasmid accessory construct having a full adenoviral genome that either lacks a packaging signal or that contains sufficient additional nucleotides to be rendered unpackagable, to produce a transformed host cell, wherein the heterologous gene encodes a human protein, Factor VIII (claim 5, column 14). Dwarki further teaches using an albumin promoter in the AAV, which is a liver-specific

promoter (column 6, lines 25-40). In addition, the use of a pharmaceutical composition can be inferred, as it would otherwise be impossible to deliver the AAV vector to a cell.

To the extent that the applicants' traversal is applicable to the new rejection under 102(e), the traversal is acknowledged and is not found persuasive for the following reasons: a claim of a patent is considered enabled, which overcomes the applicants argument that the art does not provide a reasonable expectation of success. More specifically, Dwarki teaches a gutted AAV vector, which is the same type of AAV vector that the applicants are claiming. So, the patent is not teaching away from the art. In addition, the prior art of record that was relied upon by applicant is silent about gutted AAV vectors and provides a generalization concerning a typical AAV vector (the genome of typical AAV is only 4.7kb) that is not gutted. One skilled in the art would understand the problem with AAV vectors that are not gutted as evident by Hortelano et al. (ART. CELL, BLOOD, SUBS., and IMMOD BIOTECH, Vol. 28, pp. 1-24, 2000) and would be motivated to remove any element that could be provided in trans in order to produce a gutted AAV vector comprising a nucleic acid encoding a functional Factor VIII protein as taught by Dwarki.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8, 9, 10, 16, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiorini et al. (US Patent No. 5,693,531) taken with Simonet (US Patent No. 6,268,212, filed on 1994). Chiorini teaches an AAV vector and AAV particles generated therefrom (column 1, lines 4-5 and column 8, claim 1). The vector system for producing a virus particle (virion) comprises a vector being an AAV vector, including the 5' and 3' ITRs and a heterologous sequence (column 8, claim 1). Chiorini further teaches that the DNA sequence may encode Factor VIII and be under control of a suitable promoter (column 3, lines 5-30). Chiorini does not specifically teach using a pharmaceutical composition (e.g. water) comprising the virion described above, however, it would have been obvious to one of ordinary skill in the art that the

virion was contained in a pharmaceutical composition because it is well known in the art that when using virions in an experiment, they are stored in sterile water. However, Chiorini does not teach a pharmaceutical composition comprising a recombinant AAV virion comprising a human Factor VIII subunit operably linked to a tissue specific promoter [e.g. liver-specific, HNF-3 albumin promoter or the transthyretin (TTR) gene promoter].

However, at the time the invention was made, tissue specific promoter, specifically liver-specific promoters (e.g. TTR) were well known in the art for use in enhancing liver expression of a transgene using a vector as exemplified by Simonet. Simonet teaches several liver-specific promoters (e.g. albumin or TTR) that could be used in producing a vector comprising a transgene (expressed in the liver) operably linked to a liver-specific promoter (column 3, line 64-column 4, line 12 and abstract).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention made as routine to combine the teaching of Chiorini and Simonet to make a pharmaceutical composition comprising a recombinant AAV comprising a human Factor VIII subunit operably linked to a liver specific promoter (e.g. HNF-3 albumin or TTR promoter). One of ordinary skill in the art would have motivated to make the composition because factor VIII is expressed in the liver and it is routine practice to one of ordinary skill in the art to use tissue specific promoters to increase gene expression of a vector in the tissue of interest as taught by Simonet.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicants traverse the rejection under 103(a) for the following reasons: there is no reasonable expectation of success because (1) the cited references do not even remotely enable the claimed composition, and (2) the art as a whole taught away from the claimed composition at the time of filing (see Hortelano et al. (ART. CELL, BLOOD, SUBS., and IMMOD BIOTECH, Vol. 28, pp. 1-24, 2000, Chao et al., Blood, Vol. 95, 1594-1599, 2000, and Gnatenko et al., pp. 27-36, 1999). See pages 3-5.

The applicants' traversal is acknowledged and is not found persuasive for the following reasons: Chiorini teaches a gutted AAV vector, which is the same type of AAV vector that the applicants are claiming. So, the patent is not teaching away from the art and Dwarki teaches using a gutted AAV comprising a nucleic acid sequence encoding a Factor VIII protein, which would strengthen the validity of the production of an AAV virion comprising a nucleic acid encoding a functional Factor VIII protein taught by Chiorini. In addition, the prior art of record that was relied upon by applicant is silent using gutted AAV vectors and provides a generalization concerning typical AAV vectors (the genome of typical AAV is only 4.7kb that does not encompass gutted AAV vector) and the problems of using full-size hFVIII cDNA (7kb) and truncated version of hFVIII is 4.4 kb. One skilled in the art would understand the problem with AAV vectors that are not gutted as evident by Hortelano et al. (ART. CELL, BLOOD, SUBS., and IMMOD BIOTECH, Vol. 28, pp. 1-24, 2000) and would be motivated to remove any element (e.g. rep and/or cap genes) in the AAV vector that could be provided in trans in order to produce a gutted AAV vector comprising a nucleic acid encoding a functional Factor VIII protein as taught by Chiorini.

Claims 8-13 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dwarki et al. (US Patent No. 6,221,646, effective filing date, 7/31/1997) taken with Almstedt et al. (WO 91/09122). Dwarki teaches a method of producing a replication defective recombinant AAV virions, comprising the following structure: (i) a heterologous gene operatively positioned between two AAV ITRs; (ii) an AAV helper construct having at least one gene encoding an AAV capsid protein, and (iii) an adeno-plasmid accessory construct having a full adenoviral genome that either lacks a packaging signal or that contains sufficient additional nucleotides to be rendered unpackagable, to produce a transformed host cell, wherein the heterologous gene encodes a human protein, Factor VIII (claim 5, column 14). In addition, the use of a pharmaceutical composition can be inferred, as it would otherwise be impossible to deliver the AAV vector to a cell. Dwarki further teaches using an albumin promoter in the AAV, which is a liver-specific promoter (column 6, lines 25-40). However, Dwarki does not teach a pharmaceutical composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a functional Factor VIII, wherein the nucleotide sequence comprises a heavy and a light chain, and wherein said nucleotide sequence further comprises a junction that operably links said heavy and light chain.

However, at the time the invention was made, a recombinant factor VIIII protein comprising a first DNA segment coding for the 90kDa chain and a second DNA segment coding for the 80kDa chain of human factor VIII, wherein the segments were interconnected by a linker DNA segment coding for a linker peptide of 4 to about 100 amino acid residues of the B domain of human factor VIII, at least 4 of the amino acid residues originating from the C-terminal of the domain (abstract) was well known in the art for use exemplified by Almstedt. Almstedt further

teaches that the DNA sequence can be expressed in recombinant expression vectors (abstract). In addition, Almstedt teaches that the smallest active form (one heavy chain and one light chain) with a molecular weight of 170kDa could be activated by thrombin to the same extent as the high molecular weight forms and there was an indication that that smaller form has a 50% longer survival time compared to the higher molecular form (page 4).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention made as routine to combine the teaching of Dwarki and Almstedt to make a pharmaceutical composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a functional Factor VIII taught by Almstedt, wherein the nucleotide sequence comprises a heavy and a light chain, and wherein said nucleotide sequence further comprises a junction that operably links said heavy and light chain. One of ordinary skill in the art would have motivated to make the composition because Almstedt teaches that the smaller form comprising both chains has a 50% longer in vivo survival time compared to the higher molecular forms.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

To the extent that the applicants' traversal is applicable to the new rejection under 103(a), the traversal is acknowledged and is not found persuasive for the following reasons: a claim of a patent is considered enabled, which overcomes the applicants argument that the art does not provide a reasonable expectation of success. More specifically, Dwarki teaches a gutted AAV vector, which is the same type of AAV vector that the applicants are claiming. So, the patent is not teaching away from the art. In addition, the prior art of record that was relied upon by

applicant is silent about gutted AAV vectors and provides a generalization concerning a typical AAV vector (the genome of typical AAV is only 4.7kb) that is not gutted. One skilled in the art would understand the problem with AAV vectors that are not gutted as evident by Hortelano et al. (ART. CELL, BLOOD, SUBS., and IMMOD BIOTECH, Vol. 28, pp. 1-24, 2000) and would be motivated to remove any element that could be provided in trans in order to produce a gutted AAV vector comprising a nucleic acid encoding a functional Factor VIII protein as taught by Dwarki.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
7/12/02

DAVE T. NGUYEN
PRIMARY EXAMINER